EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF); Scientific Opinion on Flavouring Group Evaluation 209 (FGE.209): Consideration of gentoxocity data on one alpha,beta-unsaturated aldehyde from chemical subgroup 2.3 of FGE.19 by EFSA

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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 209 (FGE.209):

Consideration of gentoxocity data on one alpha,beta-unsaturated aldehyde from chemical subgroup 2.3 of FGE.19 by EFSA[1]

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) to provide scientific advice to the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the Panel was requested to consider the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) evaluations of flavouring substances assessed since 2000, and to decide whether no further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. These flavouring substances are listed in the Register, which was adopted by Commission Decision 1999/217/EC and its consecutive amendments.

The present Flavouring Group Evaluation 209 (FGE.209), corresponding to subgroup 2.3 of FGE.19, concerns one cyclic aldehyde with the alpha,beta-unsaturation in conjugation with the ring system. The alpha,beta-unsaturated aldehyde and ketone structures are considered alerts for genotoxicity and the data on genotoxicity previously available did not rule out the concern for genotoxicity. Accordingly, the Panel has requested additional genotoxicity data for this substance, 2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104], according to the test strategy.

Subsequently, the Flavour Industry has performed new genotoxicity studies, and submitted *in vitro* genotoxicity data for 2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde.

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1 On request from the Commission, Question No EFSA-Q-2010-01249, adopted on 4 February 2011.

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3 Acknowledgement: The Panel wishes to thank the members of the Working Group on Genotoxicity of Flavourings for the preparation of this Opinion: Vibe Beltoft, Mona-Lise Binderup, Wilfried Bursch, Angelo Carere, Riccardo Crebelli, Karl-Heinz Engel, Rainer Gürtler, John Christian Larsen, Wim Mennes, Karin Nørby and EFSA's staff member Kim Rygaard Nielsen for the preparatory work on this scientific Opinion.

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The Panel has examined these new data and concluded based on these that the *in vitro* genotoxicity data on 2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] do not indicate genotoxic potential. 2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] will then be evaluated through the Procedure in Flavouring Group Evaluation 79, Revision 1 (FGE.79Rev1).

KEY WORDS

2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde, Safranal, FL-no: 05.104, Subgroup 2.3, FGE.19, FGE.209, Genotoxicity.

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BACKGROUND

Regulation (EC) No 2232/96 of the European Parliament and the Council (EC, 1996a) lays down a Procedure for the establishment of a list of flavouring substances, the use of which will be authorised to the exclusion of all other substances in the EU. In application of that Regulation, a Register of flavouring substances used in or on foodstuffs in the Member States was adopted by Commission Decision 1999/217/EC (EC, 1999a), as last amended by Commission Decision 2009/163/EC (EC, 2009a). Each flavouring substance is attributed a FLAVIS-number (FL-number) and all substances are divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common.

Substances which are listed in the Register are to be evaluated according to the evaluation programme laid down in Commission Regulation (EC) No 1565/2000 (EC, 2000a) which is broadly based on the Opinion of the Scientific Committee on Food (SCF, 1999a). For the submission of data by the manufacturer, deadlines have been established by Commission Regulation (EC) No 622/2002 (EC, 2002b).

After the completion of the evaluation programme the Union list of flavouring substances for use in or on foods in the EU shall be adopted (Article 5 (1) of Regulation (EC) No 2232/96) (EC, 1996a).

Flavouring Group Evaluation 19 (FGE.19) contains 360 flavouring substances from the EU Register being alpha, beta-unsaturated aldehydes or ketones and precursors which could give rise to such carbonyl substances via hydrolysis and / or oxidation (EFSA, 2008b).

The alpha, beta-unsaturated aldehyde and ketone structures are structural alerts for genotoxicity. The Panel noted that there were limited genotoxicity data on these flavouring substances but that positive genotoxicity studies were identified for some substances in the group.

The alpha, beta-unsaturated carbonyls were subdivided into 28 subgroups on the basis of structural similarity (EFSA, 2008b). In an attempt to decide which of the substances could go through the Procedure, a (quantitative) structure-activity relationship (Q)SAR prediction of the genotoxicity of these substances was undertaken considering a number of models (DEREKfW, TOPKAT, DTU-NFI-MultiCASE Models and ISS-Local Models, (Gry et al., 2007)).

The Panel noted that for most of these models internal and external validation has been performed, but considered that the outcome of these validations was not always extensive enough to appreciate the validity of the predictions of these models for these alpha, beta- unsaturated carbonyls. Therefore, the Panel considered it inappropriate to totally rely on (Q)SAR predictions at this point in time and decided not to take substances through the procedure based on negative (Q)SAR predictions only.

The Panel took note of the (Q)SAR predictions by using two ISS Local Models (Benigni & Netzeva, 2007a; Benigni & Netzeva, 2007b) and four DTU-NFI MultiCASE Models (Gry et al., 2007; Nikolov et al., 2007) and the fact that there are available data on genotoxicity, *in vitro* and *in vivo*, as well as data on carcinogenicity for several substances. Based on these data the Panel decided that 15 subgroups (1.1.1, 1.2.1, 1.2.2, 1.2.3, 2.1, 2.2, 2.3, 2.5, 3.2, 4.3, 4.5, 4.6, 5.1, 5.2 and 5.3) (EFSA, 2008b) could not be evaluated through the Procedure due to concern with respect to genotoxicity. Corresponding to these subgroups, 15 Flavouring Group Evaluations (FGEs) were established, FGE.200, 204, 205, 206, 207, 208, 209, 211, 215, 219, 221, 222, 223, 224 and 225).

For 11 subgroups the Panel decided, based on the available genotoxicity data and (Q)SAR predictions, that a further scrutiny of the data should take place before requesting additional data from the Flavouring Industry on genotoxicity. These subgroups were evaluated in FGE.201, 202, 203, 210, 212, 213, 214, 216, 217, 218 and 220. For the substances in FGE.202, 214 and 218 it was concluded that a genotoxic potential could be ruled out and accordingly these substances will be evaluated using the Procedure. For all or some of the substances in the remaining FGEs, FGE.201. 203, 210, 212, 213, 216, 217 and 220 the genotoxic potential could not be ruled out.

To easy the data retrieval of the large number of structurally related alpha,beta-unsaturated substances in the different subgroups for which additional data are requested, EFSA has worked out a list of representative substances for each subgroup (EFSA, 2008bc). Likewise an EFSA genotoxicity expert group has worked out a test strategy to be followed in the data retrieval for these substances (EFSA, 2008bb).

The Flavouring Industry has been requested to submit additional genotoxicity data according to the list of representative substances and test strategy for each subgroup.

The Flavouring Industry has now submitted additional data and the present FGE concerns the evaluation of these data requested on genotoxicity.

TERMS OF REFERENCE

The European Commission requests the European Food Safety Authority to carry out an evaluation of the data on 2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] and depending on the outcome proceed to the full evaluation of this flavouring substance, in accordance with Commission Regulation (EC) No 1565/2000.

ASSESSMENT

1. Presentation of the substance in the JECFA Flavouring Group

1.1. Description

The present Flavouring Group Evaluation 209 (FGE.209), corresponding to subgroup 2.3 of FGE.19, concerns one cyclic aldehyde with the alpha,beta-unsaturation in conjugation with the ring system. The substance under consideration in the present evalution is shown in Table 1.

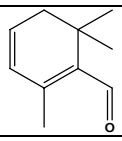
The substance has previously been evaluated by the JECFA (JECFA, 2002b), a summary of the current evalution status by the JECFA and the outcome of this consideration is presented in Table 2.

The alpha,beta-unsaturated aldehyde and ketone structures are considered alerts for genotoxicity (EFSA, 2008b) and the data on genotoxicity previously available did not rule out the concern for genotoxicity.

1.2. Representative substances for subgroup 2.3

As subgroup 2.3 of FGE.19 only concerns one substance, The Panel has requested additional genotoxicity data according to the test strategy (EFSA, 2008bb) for this substance. The substance is shown in table 1.1.

Table 1.1 Representative substance for subgroup 2.3 of FGE.19 (EFSA, 2008bc)

FL-no JECFA-no	Subgroup	EU Register name	Structural formula	FEMA no CoE no CAS no
05.104 977	2.3	2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde		3389 10383 116-26-7

2. Additionally submitted genotoxicity data on the representative substance of subgroup 2.3

Introduction

The Industry has submitted data concerning genotoxicity studies for the representative and only substance for this subgroup, 2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] (safranal).

2.1. *In vitro* data

In vitro genotoxicity assays have been performed on the alpha,beta-unsaturated aldehyde safranal [FL-no: 05.104].

2.1.1. Bacterial Reverse Mutation Assay

Safranal has been tested for its ability to induce gene mutations in the bacterial reverse mutation assay according to OECD guideline 471 (Beevers, 2010b) (for details see Table 3). The concentrations used in the different experiments were based on concentrations observed to give toxic effects in previous experiments. Positive and negative controls were included in all experiments according to current guidelines.

There were some increases in revertant numbers in TA102 in the absence and presence of S9 in the first experiment, but these were of insufficient magnitude to be considered as evidence of mutagenicity, they were not concentration-related, and were not reproducible in the other experiments. In all other strains there was no evidence of mutagenic activity either in the absence or presence of S9 in any of the experiments.

It is concluded that under the test conditions applied safranal did not induce gene mutations in bacteria.

2.1.2. Micronucleus assays

Safranal was evaluated in an *in vitro* micronucleus assay in human peripheral blood lymphocytes for its ability to induce chromosomal damage or aneuploidy in the presence and absence of S9 (Whitwell, 2010c). The maximum soluble concentration of 1250 µg/ml was selected as the maximum concentration for the cytotoxicity range finder test. The concentrations in the main tests were based on toxicity shown in this range finding study (for details see Table 3).

At the highest concentration used in the 3+21 hour treatment in the presence of S9, a small statistical increase in the frequency of micronucleated binucleate cells (MNBN) was observed, but this was set against a low mean concurrent vehicle control response. This concentration induced 62 % cytotoxicity, and there was no statistically significant increase in MNBN at the next lowest concentration, which induced 42 % cytotoxicity. Therefore, this isolated increase was not considered to be of biological importance. Outside of this isolated observation at a high level of toxicity, no evidence of chromosomal damage or aneuploidy was observed in terms of any increase in the frequency of MNBN in the presence or absence of S9.

It is concluded that under the conditions of this study, safranal did not induce micronuclei in cultured human lymphocytes.

2.2. *In vivo* data

Based on the *in vitro* data available no *in vivo* data are needed.

2.3. Discussion of Mutagenicity/Genotoxicity Data

2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] was tested for all three genetic endpoints: gene mutations, structural and numerical chromosomal aberrations. The substance did not induce gene mutations in bacteria and was not clastogenic and/or aneugenic in mammalian cells *in vitro*.

Although this flavouring substance showed evidence of cytotoxicity at high concentrations, it did not induce biologically significant genotoxic responses.

3. Conclusion

The *in vitro* genotoxicity data on 2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] do not indicate genotoxic potential. 2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] will then be evaluated through the Procedure in FGE.79Rev1.

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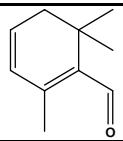
TABLE 1: SPECIFICATION SUMMARY OF THE SUBSTANCE IN THE FLAVOURING GROUP EVALUATION 206 (JECFA, 2002D)

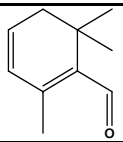
Table 1: Specification Summary of the Substance in the Present Group (JECFA, 2002d)

FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)
05.104 977	2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde		3389 10383 116-26-7	Liquid $C_{10}H_{14}O$ 150.22	Insoluble Miscible	70 (1 hPa) -NMR 96 %	1.525-1.533 0.968-0.980 (20°)

1) Solubility in water, if not otherwise stated.
2) Solubility in 95% ethanol, if not otherwise stated.
3) At 1013.25 hPa, if not otherwise stated.
4) At 20°C, if not otherwise stated.
5) At 25°C, if not otherwise stated.

TABLE 2: CURRENT SAFETY EVALUATION STATUS APPLYING THE PROCEDURE (BASED ON INTAKES CALCULATED BY THE MSDI APPROACH) (JECFA, 2002C)

Table 2: Summary of Safety Evaluation of the JECFA Substances in the Present Group (JECFA, 2002c)

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	JECFA Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (genotoxicity)
05.104 977	2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde		3.5 0.07	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Evaluated in FGE.209, genotoxicity concern could be ruled out.

1) EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/capita/day.
2) Thresholds of concern: Class I = 1800 µg/person/day, Class II = 540 µg/person/day, Class III = 90 µg/person/day.
3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
4) No safety concern based on intake calculated by the MSDI approach of the named compound.
5) Data must be available on the substance or closely related substances to perform a safety evaluation.

TABLE 3: GENOTOXICITY (*IN VITRO*)

Table 3: Summary of Additionally Submitted Genotoxicity Data on the Representative Substance of Subgroup 2.3

FL-no	Chemical Name	Test System *in vitro*	Test Object	Concentrations of Substance and Test Conditions	Result	Reference	Comments
[05.104]	2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde	Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and TA102	1.6, 8, 40, 200, 1000, 5000 µg/plate	Negative [4]	(Beevers, 2010b)	Valid study. First experiment: Standard plate ± S9. Toxicity was observed in all strains with and without S9 at 5000 µg/plate and in TA1537 and TA102 with S9 at 1000 µg/plate.
			S. typhimurium TA98, TA100, TA1535, TA1537 and TA102	125, 250, 500, 1000, 2000, 5000 µg/plate	Negative [4]		Valid study. Second experiment: Standard plate without S9. Toxicity was observed at 2000 µg/plate and above.
			S. typhimurium TA98, TA100, TA1535	62.5, 125, 250, 500, 1000, 2000, 5000 µg/plate	Negative [4]		Valid study. Second experiment with S9 and preincubation: Toxicity was observed at 500 µg/plate and above.
			S. typhimurium TA1537 and TA102	62.5, 125, 250, 500, 1000, 2000 µg/plate	Negative [4]		Valid study. Second experiment with S9 and preincubation: Toxicity was observed at 500 µg/plate and above.
			S. typhimurium TA98, TA100, TA1535, TA1537 and TA102	15.625, 31.25, 62.5, 125, 250, 500 µg/plate	Negative [4]		Valid study. Third experiment with S9 and preincubation: Toxicity was observed at 250 µg/plate and above.
		Micronucleus induction	Human peripheral blood lymphocytes	0, 40, 60, 90 µg/ml [1] 0, 80, 100, 120, 140 µg/ml [2] 0, 4, 8, 12 µg/ml [3]	Negative [5]	(Whitwell, 2010c)	Valid study.

[1] 3 hours treatment 21 hours recovery without S9.
[2] 3 hours treatment 21 hours recovery with S9.
[3] 24 hours treatment no recovery without S9.
[4] The assays were performed according to OECD guideline 471 and in compliance with GLP.
[5] This assay is performed in accordance with OECD 487.

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ABBREVIATIONS

CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CoE	Council of Europe
DMSO	Dimethyl Sulphoxide
EFFA	European Flavour and Fragrance Association
EFSA	The European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
ID	Identity
IR	Infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MNBN	MicroNucleated BiNucleate cells
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
NMR	Nuclear Magnetic Resonance
No	Number
NOAEL	No observed adverse effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
(Q)SAR	(Quantitative) Structure Activity Relationship
SCF	Scientific Committee on Food
WHO	World Health Organisation